

PROTOCOL FOR EPILEPSY SURGERY

Introduction:

Epilepsy is a common disorder of childhood. It affects 0.5% of the pediatric population, and approximately 70% of all epilepsies begin in childhood. The mainstay of treatment for epilepsy is antiepileptic drugs (AEDs). However, with the currently available medications, including the new AEDs, seizures can be satisfactorily controlled in only 70% of children.

In view of the current CRS eligibility criteria, which include treatment-resistant epilepsy, most children with epilepsy seen in the various CRS clinics have seizures that are difficult to control. Many of these patients have neurological and intellectual disability on the basis of co-morbid neurological problems, such as cerebral palsy. However, for all of these patients, and their families, poorly controlled seizures results in significant day-to-day struggles, and compromised quality of life. Intractable epilepsy has distressing medical, financial, social, and psychological consequences.

Over the years, resective brain surgery has proved to be an important alternative treatment for children with intractable epilepsy. Epilepsy surgery in specialized centers has been successful in controlling seizures in 50-80% of children undergoing surgery. It is also realized that the success of epilepsy surgery, both medically and psychosocially, is significantly better when the procedure is performed in childhood. Improved technology has made it possible to accurately identify the site of origin of seizures in the brain, making surgery feasible for more patients.

Proposals for standards and guidelines for the field of epilepsy surgery (and for epilepsy surgery in children) have evolved, beginning with the National Institutes of Health (NIH) Consensus Development Conference in 1990. As with most surgical therapies, controlled, randomized trials regarding surgical outcomes are relatively rare. Criteria for the referral and evaluation of children for surgical treatment of epilepsy have been addressed most recently by the Subcommission for Pediatric Epilepsy Surgery, Commission on Neurosurgery, of the International League Against Epilepsy (ILAE).¹ This CRS protocol rests upon these consensus statements.

There is no single definition of intractable (or treatment-resistant) epilepsy that is suitable for all patients. The decision about the need to look beyond conventional AED therapy is always highly individualized. Seizure frequency, the type of seizures, and the severity of seizure events each bear significantly on quality of life, and are thus important determinants about the need to consider epilepsy surgery. The frequency of seizures varies considerably between patients. However, even infrequent seizures may result in significant disability if they are likely to be associated with physical injury due to falls, brain injury due to status epilepticus, or social disability such as the inability to drive or work. For some patients, seizures can be controlled, but only by utilizing high doses of AEDs, which renders the patient chronically over-medicated, or prone to other significant side effects. These patients, likewise, are considered to be failures of medical management, and are potential candidates for pre-surgical evaluation. In brief, patients whose seizures are incompletely controlled, or who have unacceptable side effects of conventional AEDs, are candidates for epilepsy surgery evaluation.

The number of AEDs that must be tried to determine that the patient is refractory (or ~~%~~ treatment-resistant) has recently been the subject of several studies that have added clarity to this important question. The study of Kwan and Brodie is most frequently cited, in which newly diagnosed epilepsy patients were followed prospectively within an epilepsy specialty clinic, and outcomes with respect to AED management were determined.² In this large newly treated cohort, 47% of patients achieved seizure control with the first AED tried, 13% with the second, and only 5% with the third. This study demonstrates that the most effective AED for any patient is the first one that they try. Second, and subsequent, AED choices are much less likely to be effective, and the likelihood of effectiveness diminishes with the number of AEDs that are prescribed. This has led to a ~~%~~ three-drug rule, used by many epilepsy centers, to establish the minimum number of AEDs that qualify a patient as treatment-resistant. (Some epilepsy specialists promote a ~~%~~ two-drug rule as the minimum number of AEDs prior to epilepsy surgery, since the likelihood of success with the third drug is low.) The proper AED for the seizure type under treatment, and proper use of the AED with respect to dosage and blood levels, must be present to consider the AED trial as adequate.

Please note that this protocol does not address patient suitability for surgical placement of the vagal nerve stimulator, but is restricted to intracranial procedures.

Selection of Patients:

The following criteria should be considered in referring patients to the pediatric epilepsy specialist for consideration of epilepsy surgery:

1. The patient has refractory (treatment-resistant) epilepsy. Treatment failure is present if a) the number or severity of seizures is unacceptable to the patient, family, and treating physician, or b) AED treatment results in unacceptable side effects, including excessive sedation.
2. The patient has failed conventional management with at least three AEDs that are appropriate for the seizure type, and were used with adequate dosing.

Patients meeting the above criteria should be evaluated by one of the pediatric epilepsy specialists at CRS before initiating an evaluation as a potential candidate for epilepsy surgery. Patients will be reviewed on a case-by-case basis, either with a clinic visit with the pediatric epileptologist to determine suitability for further evaluation, or by chart review by one of the pediatric epilepsy specialists.

This evaluation will include consideration of the following issues:

1. The diagnosis of epilepsy is secure. The possibility that the clinical spells may represent a different disease process, such as syncope or psychogenic seizures, requires additional evaluation prior to initiating a pre-surgical work-up.
2. The seizure type (or types) is appropriate for consideration of epilepsy surgery. Brain resection for treatment of epilepsy is appropriate for partial, or localization-related, seizures. Epilepsy surgery for generalized seizures may be appropriate under restricted circumstances, such as corpus callosotomy for patients with frequent epileptic drop attacks.
3. Surgery should be appropriate in light of the natural history expected for each patient's seizure type and epilepsy syndrome. For example, epilepsy surgery is generally not

- indicated for benign focal epilepsies of childhood, which are expected to remit around the time of puberty.
4. The etiology of the epilepsy should be clarified if possible. Appropriate diagnostic tests should be performed in an attempt to define the structural abnormality, if present.
 5. The patient should have had a reasonable trial of at least three appropriate AEDs with adequate monitoring of compliance and effects of treatment. Exceptions to this "three-drug rule" are rare, but may include circumstances such as refractory status epilepticus in which a surgically treatable lesion is found.
 6. The family (and patient) should be fully informed of all available options for treatment. The patient and/or family must make an informed decision accepting the possibility of surgical therapy. Pre-surgical evaluation is not appropriate in circumstances where the family (or patient) is not willing to consider surgical therapy.
 7. In general, the issue of epilepsy surgery in patients with significant co-existing disorders such as profound developmental retardation, progressive neurodegenerative disease, and/or severe psychiatric disorders should be approached with sensitivity to the likelihood of benefit (improved quality of life) for the patient and family.
 8. The patient should have a reasonable potential of being a candidate for one of the available surgical procedures (as detailed below).

Evaluation of Epilepsy Surgery Candidates:

1. **Pediatric Epilepsy Program**
Epilepsy surgery for CRS patients requires that evaluation and treatment be performed under the supervision of a pediatric neurologist in an epilepsy program that provides comprehensive diagnostic and treatment services.

An epilepsy program should have the following staff and facilities¹:

- a. a pediatric neurologist with special training and expertise in the field of childhood epilepsy,
- b. a neurosurgeon with expertise in epilepsy surgery in children,
- c. technical and professional staff, and physical infrastructure, to provide for EEG services necessary for pre-surgical evaluation, including continuous inpatient video-EEG monitoring,
- d. brain imaging resources, most importantly, MRI,
- e. professional resources for neuropsychological or developmental testing, and
- f. ancillary staff, to include nursing, social services, and child life, to provide support services and referral to appropriate community agencies, as a component of the epilepsy surgery process.

Additional resources that are desirable include intraoperative cortical mapping, and non-invasive imaging modalities such as functional MRI (fMRI), positron-emission tomography (PET), single-photon emission computed tomography (SPECT), and magnetoencephalography (MEG).

2. **Rationale for Resective Surgery**
In order for resective brain surgery to be effective for patients with refractory epilepsy, the seizure focus must be located, and the risk associated with removing this region of the brain must be acceptable. Most of the testing and evaluation that goes into the

process of determining the suitability of a patient for surgery addresses one or both of these issues. Patients are good candidates for epilepsy surgery if the seizure focus has been successfully localized **and** the region is established as relatively safe to remove without causing new unacceptable deficits for the patient.

3. Testing Procedures for Pre-Surgical Evaluation

Evaluation for surgery requires several standard procedures: electroencephalography, usually with inpatient video-EEG monitoring, MR imaging of the brain, and neuropsychological testing. These core studies (often supplemented by others) provide complementary information, and concordance between these tests increases the confidence level for performing successful surgery.³

Video-EEG Seizure Monitoring:

Video-EEG recordings are studied for both interictal and ictal findings, both of which offer information with respect to seizure localization. Patients are often taken off their AEDs for seizure monitoring. The duration of monitoring is highly variable, and is dependent upon how quickly informative seizures are captured. The number of seizures that need to be studied is also highly variable, but typically six or more is a conventional goal.

For some patients, the non-invasive testing (seizure monitoring with electrodes on the scalp, MRI, and neuropsychological studies) fails to adequately localize the seizure focus. Some of these patients may then be candidates for invasive monitoring with depth electrodes, and/or subdural strips or grids. Selecting patients for intracranial monitoring is highly individualized, with careful consideration of potential risks, and the likelihood of surgical success.

1. Brain Imaging Techniques

Radiological techniques to image the brain include computerized tomography (CT), MRI, PET and SPECT scanning. MRI is clearly recognized as the most important of these modalities, and advances that have come with improved MR imaging have revolutionized the field of epilepsy surgery, particularly for children. The pre-surgical work-up often requires the use of specialized MR imaging sequences, such as protocols maximizing the likelihood of detecting cortical dysplasia, or temporal lobe abnormalities.

PET, usually with injection of flourodeoxyglucose (FDG), demonstrates the distribution of cerebral metabolism by visualizing regional glucose uptake by the brain. In patients with focal seizures, interictal PET imaging may identify the epileptogenic zone by showing a region of hypometabolism. Conversely, an ictal PET study may localize the seizure focus by demonstrating a hypermetabolic region. In some instances, PET may obviate the need for intracranial EEG monitoring, or perhaps more commonly, may help localize the correct region to be studied further with intracranial grids. PET scanning is appropriate in non-lesional cases where the brain MRI is either normal or non-specific, or in some cases where functional assessment of the %normal+brain regions is required. PET imaging for lesional cases requires approval by the Regional Medical Director.

SPECT, which measures regional cerebral blood flow, can also be a useful functional imaging technique of the brain. Since blood flow is linked to cerebral metabolism, SPECT can also be used to identify possible epileptogenic areas. It is useful to have

both an ictal and an interictal study; a change from hypoperfusion during the interictal period to hyperperfusion in the ictal period is more reliable than an abnormality in either stage alone. However, SPECT is less sensitive than PET in localizing the epileptic region.

2. Neuropsychological Testing

Detailed neuropsychological testing is essential for the evaluation of various cerebral functions, including memory and language prior to surgical treatment. It defines the degree and pattern of pre-existing neuropsychological deficits, and may assist in the localization or lateralization of the area of abnormality.

The intracarotid amobarbital (ICA) test (also known as the Wada test) is used in developmentally cooperative patients to lateralize language and memory function prior to surgical treatment, and can help determine the extent of resection once the decision to proceed with surgery has been made.

3. Additional Brain Mapping Techniques

Functional MRI (fMRI) is an increasingly accepted technique for mapping particular brain functions in selected patients⁴. Brain functions that can now be visualized (mapped) with fMRI include language, motor function, and sensory function (tactile and visual). Imaging the mesial temporal lobe structures for activation with short-term memory tasks is now also feasible. The significance of fMRI is that it may enable the pre-surgical evaluation process to skip intracranial seizure recording or an intracranial brain mapping (grid mapping) stage, or otherwise provide information that is critical for best surgical planning. In general, however, fMRI requires the participation of an awake and cooperative patient, and so its use is limited with younger children, or those with developmental or behavioral impairments.

Surgical Procedures for Specific Epilepsies:

Various types of operations are performed for treatment of epilepsy. This decision is highly individualized.

1. Temporal Lobectomy/Amygdalohippocampectomy

This procedure, in its many variations, is the single most common epilepsy procedure in the adolescent and adult population. The vast majority of such cases are for refractory epilepsy associated with mesial temporal sclerosis (MTS), which is now identifiable in many cases with high-resolution MR imaging. MTS also occurs in the childhood population, and has been described in children as young as one year of age. Long-term surgical success with this group can be as high as 80%.

2. Lesion Resection

Focal lesions affecting the neocortex commonly cause refractory epilepsy. There are many responsible pathologies, but common entities include focal cortical dysplasia, cavernous malformations, and benign tumors such as gangliogliomas and dysembryoblastic neuroepithelial tumors (DNETs). The identification of the lesion by structural imaging greatly simplifies the surgical process with respect to localization of the seizure focus. Success with this group can be as high as 70-80%.

3. Tailored Neocortical Resection

These cases, usually non-lesional by high-resolution MR imaging, usually prove to be due to focal or regional cortical malformations, and are particularly common with epilepsy surgery performed on children less than 10 years of age. Many of these patients have catastrophic epilepsy, with multiple daily seizures, and deterioration of developmental milestones.

The region of surgical resection is always highly individualized in this group, often determined by functional imaging such as PET, and guided further by the use of intracranial grid electrodes for seizure and functional mapping. Long-term success (complete seizure control) in this group is approximately 50%, although many more are significantly improved by surgery.

4. Multiple Subpial Transection

This technique is utilized for identified seizure foci affecting the neocortex when surgical resection is deemed ill advised due to the presence of the seizure focus within eloquent cortex, and the associated high risk of new neurological deficits if resection is performed. The brain surface in the affected cortical region, usually the crown of the gyrus, is incised with a probe, disrupting the horizontal fibers needed for seizure propagation, but without removing cortical tissue, and therefore preserving function. Multiple subpial transection (MST) is often paired with cortical resection in adjacent areas that are determined to be safe to remove.

5. Hemispherectomy

This procedure, and its technical variants, is usually restricted to the pediatric age range, specifically for children with catastrophic epilepsy associated with disease affecting one cerebral hemisphere. Examples of disease processes appropriate for hemispherectomy include hemimegalencephaly, porencephaly resulting from intrauterine stroke or injury, Rasmussen's encephalitis, Sturge-Weber syndrome, and others. Patients are most suitable when the contralateral hemisphere is completely normal. These patients require rehabilitation following surgery, but usually recover to their pre-operative baseline with respect to motor function on the opposite side of the body. Long-term success for this procedure can be up to 80%.

6. Corpus Callosotomy

A palliative procedure, with surgical transection of a portion of the corpus callosum, in an effort to reduce the number of drop attacks that result in injury, in patients with refractory epilepsy who are not candidates for resective surgery. This procedure is commonly performed in stages, with transection of the anterior half or two-thirds of the corpus callosum, followed by transection of the posterior half if needed. Less than 5% of patients will experience complete seizure control, but 60% may have improvement in drop attacks.

7. Gamma Knife

Gamma knife (GK) is suitable for selected lesions visualized by MR imaging that result in epilepsy. While the treatment effect may be delayed by 6-12 months, this radiosurgical technique largely avoids the complications that can occur with open surgery. GK is an

option for selected pathologies, among them hypothalamic hamartoma and arteriovenous malformations.

Surgical treatment of epilepsy has developed and progressed over the last sixty years. Advances in neurophysiology, neuroimaging, specific understanding of epilepsy mechanisms, and refinement of surgical techniques has made surgery possible for many patients with intractable epilepsy. In some patients it is the only treatment that may offer the possibility of a long-term cure. The outcome data acquired by many epilepsy centers around the world has clearly established that surgery has a major role in the treatment of intractable epilepsy.

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